with a [the] model for the molecular structure of a binding pocket of IMPDH; and

d. [developing lead compounds for an inhibitor] designing inhibitors of bacterial IMPDH based on the map of three dimensional structural information of the molecular structure of the binding pocket of IMPDH.

6. (Twice Amended) A crystalline molecule or molecular complex comprising all or any parts of a binding pocket defined by structure coordinates of IMPDH amino acids 50-56, 75-80, 229-235, 252-260, 283-286, 302-322, 343-345, 365-432 and 449-455, according to Table 7, or a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has an amino acid sequence identity for the corresponding binding pocket residues of 60% or greater relative to the *S. pyogenes* IMPDH binding pocket.

7. (Twice Amended) A crystalline IMPDH molecule defined by structural coordinates for IMPDH amino acids [comprising coordinates] from *S. pyogenes* IMPDH amino acids 50-56, 75-80, 229-235, 252-260, 283-286, 302-322, 343-345, 365-433, and 449-455.

REMARKS

I. Status of the Claims

Claims 1-8 are pending.

Claims 9-15 are withdrawn reserving the right to prosecute them in a continuing application.

Claims 3-4 and 6-7 are amended.

II. Claim 3 is Amended as an Independent Claim so is Allowable

Applicant thanks the examiner for finding claim 3 allowable if rewritten in an independent form. It has been so amended, therefore applicant requests that it is allowed.

III. Claims 2, 4, 6 and 8 Are Enabled

Claim 2 defines a standard that enables the determination of molecular structures for bacterial IMPDH enzymes. It is uncertain what component of claim 2 the examiner is targeting as the basis for rejection, because there is no explanation for the rejection.

Those of skill in the art know that a well diffracted crystal is the essential element in provided x-ray diffraction patterns. The present invention provides the well diffracting crystals and discloses methods for x-ray diffraction patterns.

Rejection based on the generation of well diffracting crystals. The specification clearly provides details on screening procedures used to obtain such crystals. Furthermore various screening systems for the generation of crystals are available from commercial suppliers such as Hampton Research and Emerald Biosystems. These methods are well known to those skilled in

the art are have been used to generate crystals currently deposited in the Protein Data Bank. Because the generation of crystal is stochastic process, the methods outlined in the specification represent the accepted approach for the generation of well diffracting crystals. If necessary publications and/or declaration from experts can be submitted to support enablement.

Rejection based on the structure determination. The technique of molecular replacement is well known to those skilled in the art and can be used obtaining initial phasing for an unknown structure from a known, structurally related molecule (J.P. Turkenburg and E.J. Dodson Modern developments in molecular replacement. *Curr. Opin. Struct. Biol.* 1996 Oct;6(5):604-10).

Claim 4 is enabled. The examiner has not explained why the previous arguments supported by exhibits A and B were not persuasive that claim 4 is enabled. Therefore, the applicant repeats that argument and re-submits the exhibits herein for consideration. Claims in question have been amended to claim a method for designing inhibitors that uses the molecular information relating to the bacterial IMPDH binding pocket.

A variety of molecular docking programs are available (two are provided herein as Exhibits A and B) to enable those skilled in the art to screen compounds to identify potential inhibitors. These programs are a common component of most structural biology software (e.g. Insight II from Molecular Simulations Inc.). Most of the newer programs provide for automated docking of ligands to receptors in the structure-based drug design process. A variety of purine analogues and mammalian inhibitors have been reported in the literature and would be likely candidates to begin a search for specific inhibitors of bacterial IMPDH enzymes. However, universities (*e.g.* University of Georgia) and commercial entities (Vertex Pharmaceuticals) have, and are continuing to construct, small molecule digital libraries. The present invention provides the structural coordinates of bacterial IMPDH that enables the screening of these candidate compounds/digital libraries.

Similar arguments apply to the enablement of claim 8. Claim 8 relates a component of the binding pocket IMP that interacts with the binding pocket residues defined in claim 4.

The examiner requested further information on the structural requirements for the functional homologues that are set forth in Claim 6 (Action, pg. 3).

The rejection of claim 6 focuses on the homology argument. The specification and references cited therein define differences between bacterial and eukaryotic IMPDH enzymes. These references and the site-specific mutagenesis experiments presented in the specification demonstrate that the biochemical and kinetic differences between bacterial and eukaryotic enzymes are a consequence of the variance of specific amino acid residues. The examiner appears to take issue with the lack of specificity inherent in the use of homology criterion. Claim

6 is amended to incorporate the specific structural coordinates outlined in claim 5. The basis for this approach is outlined in the specification (page 2). The section describes the generation of a phylogenetic tree based on the homology between a global set of aligned IMPDH sequences. A subset of those aligned sequences is presented in the attached document: IMPDH sequence align.doc (Exhibits C and D). IMPDH coding region sequences were obtained from the public databases and the alignment generated using the phylogenetic analysis software provided by the University of Wisconsin Genetics Computer Group (GCG package). The table in Exhibit D was generated from the alignment data.

Application of the binding pocket definitions outlined in claim 5 are a useful measure for the use of homology to delineate specific characteristics of the IMPDH enzyme. This analysis is summarized in the attached table that summarizes the amino acid residue identify of the IMPDH binding pocket. This table demonstrates there is a reliable difference between bacterial and eukaryotic IMPDH proteins in the homology level of the binding pocket residues (an average of 71 vs. 40% identity). This difference is the basis for the biochemical and kinetic differences describe in the specification. Inclusion of additional bacterial or eukaryotic representatives would not change the outcome since the selected representatives represent the polygenetic diversity of these domains. The 60%sequence identity referenced in claim 5 represents a conservative threshold for bacterial IMPDH proteins.

IV. Claim 7 is Amended

Claim 7 is amended to answer the examiner's query how a molecule can "comprise coordinates." "Comprise" is explained by "defined by."

V. Claims 5, 6 and 8 are Not Anticipated by Sintchak Because Not All Elements of These Claims are Taught by Sintchak

The *S. pyogenes* with Chinese hamster IMPDH enzymes show only a 35% identity with Chinese hamster IMPDH of Sintchak. This level of homology did not enable interpretation of the *S. pyogenes* model (specification page 19, lines 24-28). A similar case was observed for the structure of IMPDH from *Tritrichomonas foetus* that shows a similar level of identity to the *S. pyogenes* and Chinese hamster enzymes. If molecular replacement cannot be used for determination of the structure, the information used by Sintchak cannot be used to delineate the structure of the bacterial IMPDH enzymes. Molecular replacement is generally only applicable for homologues with identity >50%. Homologues with lower identity can not reliably be used to determine structure of homologues used for building of a model as is described in the specification.

VI. Wilson Does not Teach the Same IMPDH

Wilson relates IMPDH Type II. Mammals have two form of IMPDH (Type I and II). Bacteria have only a single IMPDH enzyme. There is only 35% identity between the bacterial and both human enzymes making it impossible to use the crystal model of Wilson to solve the bacterial IMPDH molecule structures.

VII. Other Issues

Withdrawn claims now have properly designated claim 15, erroneously numbered claim 9 in a previous Amendment.

VIII. Summary and Conclusion

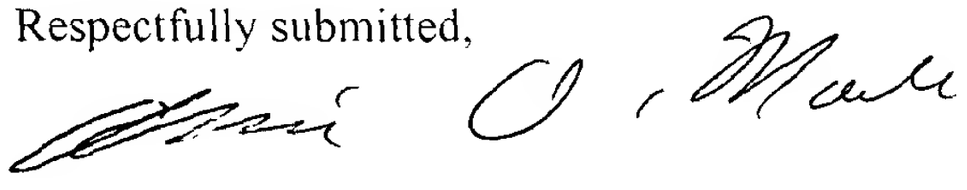
For the reasons stated above, applicant requests allowance of all pending claims.

Applicant's request a telephone interview to discuss remaining matter.

Please contact applicants' representative if you have any questions.

No other fees are believed due at this time, however, please charge any deficiencies or credit any overpayments to deposit account number 10-0435 with reference to our attorney docket number (21416-90042).

Respectfully submitted,



Alice O. Martin
Registration No. 35,601

BARNES & THORNBURG
2600 Chase Plaza
10 South LaSalle Street
Chicago, IL 60603
(312) 214-8316

MARKED UP VERSION OF CLAIMS
FOR SERIAL NO. 09/533,466

WE CLAIM:

1. A crystal of IMPDH (ionisine monophosphate dehydrogenase) isolated from a bacterial preparation.

2. The crystal of claim 1 further characterized by ability to provide x-ray diffraction patterns useful to define molecular structures for bacterial IMPDH enzymes.

3. (Amended) [The crystal of claim 1] A crystal of IMPDH (ionisine monophosphate dehydrogenase) isolated from a bacterial preparation wherein the bacterial preparation is a pure culture of *Streptococcus pyogenes*.

4. (Twice Amended) A method for designing inhibitors [developing lead compounds for an inhibitor] of bacterial IMPDH (inosine monophosphate dehydrogenase), said method comprising:

a. obtaining a crystal of bacterial IMPDH;

b. recording x-ray diffraction data from said crystal;

c. using said diffraction data to generate an electron density map consistent with a [the] model for the molecular structure of a binding pocket of IMPDH; and

d. [developing lead compounds for an inhibitor] designing inhibitors of bacterial IMPDH based on the map of three dimensional structural information of the molecular structure of the binding pocket of IMPDH.

5. A crystalline molecule or molecular complex comprising an IMPDH binding pocket defined by the structural coordinates of IMPDH amino acids 50-56, 75-80, 229-235, 252-260, 283-286, 302-322, 343-345, 365-433, and 449-455 according to Table 7 or a homologue of said molecule or molecular complex.

6. (Twice Amended) A crystalline molecule or molecular complex comprising all or any parts of a binding pocket defined by structure coordinates of IMPDH amino acids 50-56, 75-80, 229-235, 252-260, 283-286, 302-322, 343-345, 365-432 and 449-455, according to Table 7, or a homologue of said molecule or molecular complex, wherein said homologue comprises a binding

pocket that has an amino acid sequence identity for the corresponding binding pocket residues of 60% or greater relative to the *S. pyogenes* IMPDH binding pocket.

7. (Twice Amended) A crystalline IMPDH molecule defined by structural coordinates for IMPDH amino acids [comprising coordinates] from *S. pyogenes* IMPDH amino acids 50-56, 75-80, 229-235, 252-260, 283-286, 302-322, 343-345, 365-433, and 449-455.

8. A crystalline IMPDH molecule having (inosine monophosphate) IMP in its binding pocket.

15. A computer generated representation of a molecule or molecular complex comprising a binding pocket defined by the following structural coordinates of *S. pyogenes* IMPDH amino acids 50-56, 75-80, 229-235, 252-260, 283-286, 302-322, 343-345, 365-433, and 449-455.